77. The method of claim 75, wherein said CD28 ligand is an anti-CD28 antibody.

78. The method of claim 75, wherein said HIV-1 fusion cofactor is CCR5.

79. The method of claim 75, wherein said HIV-1 fusion cofactor is CXCR4.

80. The method of claim 77, wherein said anti-CD28 antibody is immobilized on a solid surface.

81. The method of claim 77, wherein said anti-CD28 antibody is soluble.

82. The method of claim 1, wherein said T cell is activated.

83. The method of claim 1, wherein said CD28 ligand is an anti-CD28 antibody.

84. The method of claim 1, wherein said HIV-1 fusion cofactor is CXCR4.

85. The method of claim 3, wherein said anti-CD28 antibody is immobilized on a solid surface.

86. The method of claim 3, wherein said anti-CD28 antibody is soluble.

REMARKS

Claims 1-54 were pending in the application. Claims 2-54 have been cancelled without prejudice, claim 1 has been amended, and new claims 55-86 have been added. Accordingly, claims 1 and 55-86 are currently pending. For the Examiner's convenience all of the claims under consideration are set forth in Appendix A.

Support for the amendments to the claims can be found throughout the specification including the originally filed claims. Specifically, support for the amendments to the claims can be found at, for example, page 37, lines 33-35 of the specification.

At paragraph 3 of the present Office Action, the Examiner has indicated that the title of the invention is not descriptive and has requested that Applicants provide a new title that is

clearly indicative of the invention to which the claims are directed. Applicants have amended the title of the application accordingly.

No new matter has been added. Any amendments to and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicants reserve the right to pursue the claims as originally filed in this or a separate application(s).

Restriction Requirement

In the Response to Restriction Requirement dated June 29, 1999, Applicants had elected the Group I invention (claims 1-***5*** and 8-20) "drawn to methods of upregulating/***modulating*** HIV-fusion cofactor expression." Applicants respectfully submit that claim 5 is directed to the method of claim 1, wherein the HIV-1 fusion cofactor expression is ***down regulated***. Applicants' intent was to elect the invention directed to methods for modulating, *e.g.*, downregulating, HIV-1 fusion cofactor expression.

Accordingly, Applicants respectfully request that the Examiner consider the invention directed to methods for downregulating HIV-1 fusion cofactor expression. Applicants respectfully submit that the same field of search is involved in the methods for downregulating as well as the methods for upregulating HIV-1 fusion cofactor expression and that, thus, no undue burden will be imposed on the Examiner. The arguments and amendments presented herein are based on the election of the invention directed to methods for downregulating HIV-1 fusion cofactor expression.

Rejection of Claims 1, 2, 4, and 8-15 Under 35 U.S.C. §112, First Paragraph

The Examiner has rejected claims 1, 2, 4, and 8-15 under 35 U.S.C.§ 112, first paragraph, as "containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention." Specifically, the Examiner is of the opinion that "[t]here is

insufficient guidance and direction in the specification as filed on how to increase HIV-1 cofactor expression (e.g. CCR5) on the surface of a T cell either in vitro or in vivo, or to increase HIV1 fusion cofactor expression on the surface of a T cell in a practical manner either in vitro or in vivo" and that "[e]xcept for cryptic sentences in the Summary of the Invention (see page 2); there does not appear to any further disclosure of such methods to increase HIV-1 fusion cofactor expression." The Examiner further notes "the elected species of anti-CD28 antibodies that are employed to stimulate accessory molecules on the surface of T cells result in downregulating HIV-1 fusion cofactor expression (see Summary of the Invention; Uses of the Invention)."

Applicants respectfully submit that in view of the amendments to the claims, the aforementioned rejection has been rendered moot. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection. Although Applicants submit that there is sufficient descriptive support in the specification as filed to satisfy section 112, first paragraph, Applicants have amended the claims to expedite prosecution. Any amendments to and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application.

Rejection of Claims 1, 2, 4, and 8-15 Under 35 U.S.C. § 112, First and Second Paragraphs

The Examiner has rejected claims 1, 2, 4, and 8-15 under 35 U.S.C. § 112, first and second paragraphs, because, according to the Examiner, "the claimed invention is not described in such full, clear, concise and exact terms as to enable any person skilled in the art to make and use the same, and/or for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention."

A) HIV-1 fusion cofactor (claims 1, 2, and 8-15):

Regarding the term "HIV-1 fusion cofactor", the Examiner is of the opinion that "[t]he instant claims are indefinite in the recitation of "HIV-1 fusion cofactor" because the characteristics of the "HIV-1 fusion cofactor(s)" are not known." The Examiner argues that "[t]his language is vague and indefinite because the metes and bounds of said 'HIV-1 fusion

cofactor(s)' are not clearly delineated and it is not apparent from the disclosure which particular 'cofactor(s)' are being referred to; other than CCR5," that "Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies the 'HIV-1 fusion cofactor(s)' encompassed by the claimed invention," and that "[w]hile the name itself may have some notion of the activity of the protein, there is nothing in the claims which distinctly claims the 'HIV-1 fusion cofactor.'"

The Examiner further argues that

> [t]here is insufficient direction or guidance provided to assist one skilled in the art in the selection of any "HIV-1 fusion cofactor" nor is there sufficient evidence provided that any such "HIV-1 fusion cofactor(s)" could be used in a practical manner either in vitro or in vivo as subject to the manipulation of an accessory molecule such as CD28 on the surface of a T cell. It would require undue experimentation to investigate all such possible "HIV-1 cofactor(s)" without more explicit guidance from the disclosure. Applicant has failed to enable or provide sufficient guidance and direction to determine the extent of "HIV-1 fusion cofactor(s)", nor is there is sufficient direction and guidance how to use any such "HIV-1 fusion cofactor(s)" in the claimed methods, including their nexus to costimulatory molecules such as CD28. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. It appears that undue experimentation would be required of one skilled in the art to practice the claimed methods with any "HIV-1 fusion cofactor(s)" commensurate in scope with the claimed invention using the teaching of the specification. Without such guidance, targeting costimulatory signals to increase HIV-1 fusion cofactor expression would be unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. Applicant's limiting the "HIV-1 fusion cofactor" to CCR5, as the only HIV-1 fusion cofactor disclosed in the specification as filed, would obviate this 35 USC, 112,first and second paragraph, rejection.

Applicants respectfully traverse the aforementioned rejection for the following reasons. Applicants respectfully submit that, in contrast to the Examiner's assertions, the term "HIV-1 fusion cofactor" is clear and definite, in that this term is well known and accepted in the art. As demonstrated by Bleul C. C. *et al.* (1996) Nature 29;382(6594):829-33 and Doranz B.J. *et al.* (1996) Cell 85(7):1149-58, submitted herewith as Appendices B and C, respectively, the term "HIV-1 fusion cofactor" is well known and accepted in the art to refer to molecules, *e.g.*,

receptors, that aid in the fusion of HIV-1 with T cells. Several HIV-1 fusion cofactors were known at the time of Applicants' invention, including the CCR5 and CXCR4/Fusin cofactors taught by Applicants' specification at, for example, page 37, lines 33-35. Thus, an ordinarily skilled artisan reading Applicants' specification at the time of filing of the invention, would have known what HIV-1 fusion cofactors are and would have also been able to practice Applicants' invention with only routine experimentation. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

B) Accessory molecule (claims 1, 2, 4, 8-15):

Regarding the term "accessory molecule", the Examiner is of the opinion that "[t]he instant claims are indefinite in the recitation of 'accessory molecule' because the characteristics of the 'accessory molecule(s)' are ambiguous and unclear", that "[t]his language is vague and indefinite because the metes and bounds of said 'accessory molecule(s)' are not clearly delineated", and that "Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies the 'accessory molecule(s)' encompassed by the claimed invention."

Applicants respectfully submit that in view of the amendments to the claims, the aforementioned rejection has been rendered moot. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection. Any amendments to and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application.

C) An agent which interacts with the accessory molecule (claim 13)

Regarding the term "agent", the Examiner is of the opinion that "[t]he instant claims are indefinite in the recitation of 'agent' because the characteristics of the 'agent(s)' are not known" and that "[t]his language is vague and indefinite because the metes and bounds of said 'agent(s)' are not clearly delineated and it is not apparent from the disclosure which particular 'agent(s)' are

being referred to, " and that "Applicant has not provided sufficient biochemical information (e.g. molecular weight, amino acid composition, N-terminal sequence, etc.) that distinctly identifies the 'agent(s)' encompassed by the claimed invention."

Applicants respectfully submit that in view of the amendments to the claims, the aforementioned rejection has been rendered moot. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection. Any amendments to and/or cancellation of the claims should in no way be construed as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application.

Rejection of Claims 1, 2, 4, and 8-15 Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 1, 2, 4, and 8-15 under 35 U.S.C. § 112, second paragraph, as "being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." In particular, the Examiner is of the opinion that "[t]he claimed methods do not set forth clear, distinct and positive process steps, including providing the appropriate reagents/elements to carry out the claimed methods, including a resolution or correlating step that clearly relates to the preamble of the claim (claims 1, 2, 4, 8-15)."

The Examine argues that claims "1, 2, 4 and 11-15 are indefinite in [the] recitation of "modulating" because it is ambiguous as to the direction (positive or negative) or degree of said modulating" and that "the claims are indefinite in that they recite non-elected limitations (e.g. modulating as it reads on downregulating) and does not clearly recited the elected invention, drawn to increasing HIV-1 fusion cofactor expression."

Applicants respectfully submit that in view of the amendments to the claims (amended to be directed to the elected invention), the aforementioned rejection has been rendered moot. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw this rejection. Any amendments to and/or cancellation of the claims should in no way be construed

as an acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application.

Rejection of Claims 1, 2, 4, 8-10, and 12-15 Under 35 U.S.C. § 102(b) Over Smithgall et al.

The Examiner has rejected claims 1, 2, 4, 8-10, and 12-15 under 35 U.S.C. § 102(b) as being anticipated by Smithgall *et al.* (AIDS Research and Human Retroviruses 11: 885 - 892, 1995;.1449). The Examiner relies on Smithgall *et al.* for teaching "costimulation of T cells with CD28-specific antibodies, which modulates HIV infection and replication in vitro." The Examiner argues that "no more of the reference is required than that it sets forth the substance of the invention" and that "[t]he claimed functional limitations would be inherent properties of the referenced methods, which use the CD28-specific antibodies to treat T cell antibodies, resulting in increased virus replication, encompassed by the claimed methods. Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993)."

Applicants respectfully traverse this rejection for the reasons discussed in detail below.

As amended, the claims are directed to *in vivo* and *in vitro* methods for downregulating HIV-1 fusion cofactor, *e.g.*, CCR5 or CXCR4, expression in a T cell by contacting the T cell *in vivo* or *in vitro* with a CD28 ligand.

For a prior art reference to anticipate in terms of 35 U.S.C. § 102 a claimed invention, the prior art must teach ***each and every element*** of the claimed invention. Lewmar Marine v. Barient, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Smithgall *et al.* do not teach or suggest each and every element of the claimed invention in that that Smithgall *et al.* do not teach or suggest methods for downregulating HIV-1 fusion cofactor, *e.g.*, CCR5 or CXCR4, expression in a T cell by contacting the T cell *in vivo* or *in vitro* with a CD28 ligand. Smithgall *et al.* "explore the role of costimulation of T cells via CD28 in HIV-1 replication" and report that their "*in vitro* results suggest that CD28 plays a central role in HIV-1 replication and that interfering with the CD28 costimulatory pathway may modify the

course of HIV-1 infection" (see the Abstract at page 885). There is no teaching in Smithgall *et al.* regarding HIV-1 fusion cofactors or the effect of CD28 on HIV-1 fusion cofactor expression.

To the extend that the Examiner appears to take the position "would be inherent properties of the referenced methods", Applicants respectfully submit that "[t]he fact that a certain result or characteristic ***may*** occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re* Rijkaert, 9F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)." Moreover, "[t]o serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence" and "[s]uch evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20 USPQ2d 1746, 1749 (Fed. Cir. 1991). Applicants respectfully submit that the Examiner has not made it clear that the missing matter, *e.g.*, an HIV-1 fusion cofactor such as CCR5, is described in Smithgall *et al.* and that persons of ordinary skill in the art would so recognize at the time of Applicants' invention.

Since Smithgall *et al.* fail to teach every element of the currently pending claims, Applicants respectfully request that this section 102(b) rejection, be reconsidered and withdrawn.

Rejection of Claims 1, 2, 4, 8-10, and 12-15 Under 35 U.S.C. § 102(b)

Over Pinchuk et al.

The Examiner has rejected claims 1, 2, 4, 8-10, and 12-15 under 35 U.S.C. § 102(b) as being anticipated by Pinchuk *et al.* (Immunity 1: 317 - 325, 1994; 1449). The Examiner relies on Pinchuk *et al.* for teaching costimulation of T cells with CD28-specific antibodies, which modulates HIV infection and replication in vitro. The Examiner is of the opinion that "no more of the reference is required than that it sets forth the substance of the invention" and that "[t]he claimed functional limitations would be inherent properties of the referenced methods, which use

the CD28 specific antibodies to treat T cell antibodies, resulting in increased virus replication, encompassed by the claimed methods. Also, see Ex parte Novitski 26 USPQ 1389 (BPAI 1993)."

Applicants respectfully traverse this rejection for the reasons discussed in detail below.

As amended, the claims are directed to *in vivo* and *in vitro* methods for downregulating HIV-1 fusion cofactor, *e.g.*, CCR5 or CXCR4, expression in a T cell by contacting the T cell *in vivo* or *in vitro* with a CD28 ligand.

For a prior art reference to anticipate in terms of 35 U.S.C. § 102 a claimed invention, the prior art must teach ***each and every element*** of the claimed invention. Lewmar Marine v. Barient, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Pinchuk *et al.* do not teach or suggest each and every element of the claimed invention in that Pinchuk *et al.* do not teach or suggest methods for downregulating HIV-1 fusion cofactor, *e.g.*, CCR5 or CXCR4, expression in a T cell by contacting the T cell *in vivo* or *in vitro* with a CD28 ligand. Pinchuk *et al.* investigate "the role of blood dentritic cells (DCs) in transmission of HIV-1 from infected to uninfected CD4+ T cells, and the accessory molecules involved" and report that their "data suggest a linkage between CD40-CD40L and CD28-CD80 counterreceptors on DCs and T cells, and spread of HIV infection in vivo" (see the Abstract at page 317). There is no teaching in Pinchuk *et al.* regarding HIV-1 fusion cofactors or the effect of CD28 on HIV-1 fusion cofactor expression.

To the extend that the Examiner appears to take the position "would be inherent properties of the referenced methods", Applicants respectfully submit that "[t]he fact that a certain result or characteristic ***may*** occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re* Rijkaert, 9F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993)." Moreover, "[t]o serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence" and "[s]uch evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268, 20

USPQ2d 1746, 1749 (Fed. Cir. 1991)." Applicants respectfully submit that the Examiner has not made it clear that the missing matter, *e.g.*, an HIV-1 fusion cofactor such as CCR5, is described in Pinchuk *et al.* and that persons of ordinary skill in the art would so recognize at the time of Applicants' invention.

Since Pinchuk *et al.* fail to teach every element of claims the currently pending claims, Applicants respectfully request that this section 102(b) rejection, be reconsidered and withdrawn.

CONCLUSION

Reconsideration and allowance of all the pending claims is respectfully requested. If a telephone conversation with Applicants' Attorney would expedite prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 227-7400.

Respectfully submitted,

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Dated: March 27, 2000

APPENDIX A

1. A method for downregulating HIV-1 fusion cofactor expression in a T cell, comprising contacting the T cell with a CD28 ligand *in vitro*, thereby downregulating HIV-1 fusion cofactor expression in the T cell.

55. A method for downregulating CCR5 expression in a T cell, comprising contacting the T cell with a CD28 ligand *in vitro*, thereby downregulating CCR5 expression in the T cell.

56. The method of claim 55, wherein said T cell is activated.

57. The method of claim 55, wherein said CD28 ligand is an anti-CD28 antibody.

58. The method of claim 57, wherein said anti-CD28 antibody is immobilized on a solid surface.

59. The method of claim 57, wherein said anti-CD28 antibody is soluble.

60. A method for downregulating CCR5 expression in a T cell, comprising contacting the T cell with a CD28 ligand *in vivo*, thereby downregulating CCR5 expression in the T cell.

61. The method of claim 60, wherein said T cell is activated.

62. The method of claim 60, wherein said CD28 ligand is an anti-CD28 antibody.

63. The method of claim 62, wherein said anti-CD28 antibody is immobilized on a solid surface.

64. The method of claim 62, wherein said anti-CD28 antibody is soluble.

65. A method for downregulating CXCR4 expression in a T cell, comprising contacting the T cell with a CD28 ligand *in vitro*, thereby downregulating CXCR4 expression in the T cell.

66. The method of claim 65, wherein said T cell is activated.

67. The method of claim 65, wherein said CD28 ligand is an anti-CD28 antibody.

68. The method of claim 67, wherein said anti-CD28 antibody is immobilized on a solid surface.

69. The method of claim 67, wherein said anti-CD28 antibody is soluble.

70. A method for downregulating CXCR4 expression in a T cell, comprising contacting the T cell with a CD28 ligand *in vivo*, thereby downregulating CXCR4 expression in the T cell.

71. The method of claim 70, wherein said T cell is activated.

72. The method of claim 70, wherein said CD28 ligand is an anti-CD28 antibody.

73. The method of claim 72, wherein said anti-CD28 antibody is immobilized on a solid surface.

74. The method of claim 72, wherein said anti-CD28 antibody is soluble.

75. A method for downregulating HIV-1 fusion cofactor expression in a T cell, comprising contacting the T cell with a CD28 ligand *in vivo*, thereby downregulating HIV-1 fusion cofactor expression in the T cell.

76. The method of claim 75, wherein said T cell is activated.

77. The method of claim 75, wherein said CD28 ligand is an anti-CD28 antibody.

78. The method of claim 75, wherein said HIV-1 fusion cofactor is CCR5.

79. The method of claim 75, wherein said HIV-1 fusion cofactor is CXCR4.

80. The method of claim 77, wherein said anti-CD28 antibody is immobilized on a solid surface.

81. The method of claim 77, wherein said anti-CD28 antibody is soluble.

82. The method of claim 1, wherein said T cell is activated.

83. The method of claim 1, wherein said CD28 ligand is an anti-CD28 antibody.

84. The method of claim 1, wherein said HIV-1 fusion cofactor is CXCR4.

85. The method of claim 3, wherein said anti-CD28 antibody is immobilized on a solid surface.

86. The method of claim 3, wherein said anti-CD28 antibody is soluble.